Neonatal Skin Emergencies

Mark Siegel, MD; and Lara Wine Lee, MD, PhD

ABSTRACT

Although the majority of neonatal skin rashes can be safely monitored without intervention, there are a significant few that are dermatologic emergencies. When called to assess a neonate, it is important to distinguish what requires immediate diagnosis and treatment from those that represent benign etiologies. The skin may be the first clue to certain infections such as herpes simplex virus, syphilis, varicella, cytomegalovirus, fungal infections, and staphylococcal scalded skin syndrome, all of which require immediate testing and some of which may lead to severe sequelae. Cutaneous findings in neonates may also indicate the need for further evaluation. Purpura fulminans, sclerema neonatorum, neonatal lupus, and blueberry muffin rash can be indications of other underlying disorders and are reviewed as well. This article outlines these potential neonatal dermatologic emergencies and highlights the important clinical clues to each. **[*Pediatr Ann*. 2019;48(1):e36-e42.]**

The pediatrician is rarely called on for true dermatological emergencies; however, when emergencies do occur the pediatrician must be prepared to initiate a rapid assessment and treatment. Several critical infectious, neoplastic, and autoimmune processes are reviewed in this article.

CONGENITAL HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) was quantified in a recent study to occur in 9.6 per 100,000 live births in the United States.[1] It is transmitted most commonly from primary maternal infection during vaginal delivery but can also be transferred in-utero and postnatally. For mothers with active recurrent disease, the American College of Obstetrics and Gynecology[2] recommends suppressive viral therapy starting at 36 weeks of gestation. Cesarean delivery is recommended when active genital lesions or prodromal symptoms are present at the time of delivery. For those with a history of HSV but without active lesions, cesarean delivery is not indicated.

In one series, up to 70% of intrauterine infections caused vesicular lesions in the neonate and about one-third led to scar formation.[3] Babies can present with aplasia cutis-like lesions or extensive erosions mimicking epidermolysis bullosa. The scalloped borders and intact vesicles in HSV can help differentiate the two. Affected neonates frequently have central nervous system (CNS) involvement.

Perinatal infection presents in three overlapping syndromes: skin, eye, mouth (SEM); disseminated; and CNS disease. SEM accounts for 45% of neonatal HSV infections and usually occurs earliest, within the first 2 weeks of life.[4] Cutaneous lesions include clustered 2- to 4-mm vesicles and erosions with erythema (**Figure 1**). Lesions occur in areas that contacted the cervix for a prolonged time during delivery or at sites of fetal scalp monitor leads. Shallow ulceration, sized similarly to cutaneous vesicles, may occur on the mucosa as well. Skin lesions may present in disseminated or CNS syndromes.

Disseminated HSV occurs around 11 days of postnatal life and may occur even with appropriate therapy. Involvement of the brain, liver, lung, and multiple organs is common. The high mortality rate of about 75% is only slightly improved with appropriate treatment, and neurologic sequelae are common. Preterm neonates have a higher risk of dissemination.[5]

HSV encephalitis presents later, around day 17. Only up to 60% of infants will have skin involvement, making diagnosis difficult.[5] Common signs are nonspecific but include irritability and seizures. The diagnosis depends on diagnostic testing of cerebrospinal fluid (CSF).

All suspected cases should include polymerase chain reaction (PCR) testing via surface samples from the mouth,

Mark Siegel, MD, is a Resident, Department of Pediatrics, Medical University of South Carolina. Lara Wine Lee, MD, PhD, is an Assistant Professor, Department of Pediatrics and Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina.

Address correspondence to Lara Wine Lee, MD, PhD, Department of Dermatology, Medical University of South Carolina, 135 Rutledge Avenue, MSC 578, Charleston, SC 29425; email: winelee@musc.edu.

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nasopharynx, conjunctiva, and anus, in addition to CSF and whole blood. Swabs of unroofed vesicles or erosions can be sent for PCR testing and/or culture. HSV immunoglobulin (Ig) M is not sensitive, but depending on the timing there may be rising HSV IgG titers. CNS involvement relies on PCR assay of CSF, with both the sensitivity and specificity ranging from 75% to 100%.[6]

Treatment for SEM disease is parenteral acyclovir for at least 14 days. CNS involvement requires 21 days of treatment. If ocular involvement is noted, antiviral drops such as 1% trifluridine should be added.[7] One-half of infected infants will have cutaneous recurrence, and daily suppressive oral acyclovir is recommended for prevention for 6 months.[8] Of note, as there is no liquid version of valacyclovir it is not recommended in young infants.

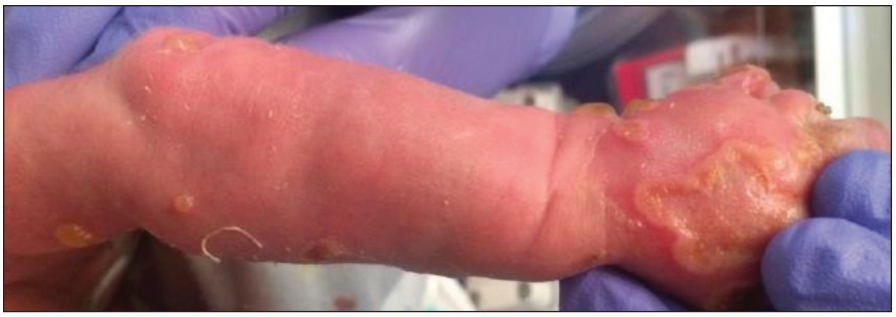

Figure 1. Bullae and vesicles involving the upper extremity of a neonate presenting with disseminated herpes simplex virus infection. Note the large, scalloped-edged bulla on the hand.

FUNGAL INFECTIONS

Candida and *Aspergillus* are the most common causes of cutaneous fungal infections, especially in premature and immunocompromised infants.[9] Superficial candidal infections are not uncommon in immunocompetent neonates and readily improve with topical antifungals; they can be severe and life-threatening, however, especially in immunocompromised hosts. Risk factors for serious infection include low birthweight, prematurity, broad-spectrum antibiotic therapy, prolonged endotracheal intubation, tracheostomy, prior fungal infections, or recent or prolonged steroid therapy;[10] hence, most of the neonatal intensive care unit population is at risk.

Congenital candidiasis presents in the first days of postnatal life and is frequently acquired in-utero.[11] It presents as an erythematous monomorphous papulovesicular eruption that progresses to pustules, crusting, and desquamation (**Figure 2A**). Despite the commonality of vaginal colonization, transmission to healthy infants is relatively uncommon, and when infection does occur the prognosis is generally excellent.[11]

In contrast, invasive fungal infections present as erosive crusting lesions with invasion into the epidermis and sometimes the dermis. Systemic involvement is also more common in premature and low-birth–weight infants. Cutaneous findings are variable with erosive dermatitis in addition to red, scaly, or vesiculopustular eruptions (**Figure 2B**). A widespread rash in premature or ill infants, respiratory distress in the immediate postnatal period, and/or leukocytosis should alert the physician to the potential for systemic candidiasis despite negative blood cultures. Invasive fungal infections may be a sign of primary immunodeficiency in a full-term neonate.

Aspergillus species are saprophytic fungi and rarely infect healthy children. Infection can be limited to the skin and is associated with intravenous catheters or prolonged occlusion by tape or monitor leads.[9] Localized areas of erythema evolve into a dark-red plaque with pustules and often a black eschar. Diagnosis is by histology and tissue culture from a lesional biopsy. Aspergillosis can disseminate to the pulmonary, gastrointestinal, or CNS tissues without primary skin infection, but a morbilliform eruption that sometimes turns pustular may be seen with systemic infection. Systemic antifungal therapy with voriconazole or amphotericin B is indicated. Surgical excision of primary skin lesions may also be warranted. Systemic aspergillosis has significantly higher mortality than primary cutaneous (near 100% vs 27%).[12]

Zygomycoses are a class of fungi including six fungi that cause disease in humans: *Rhizopus*, *Cunninghamella*, *Mucor*, *Rhizomucor*, *Saksenea*, and *Absidia*. Direct skin inoculation is the cause of primary cutaneous zygomycosis. Like aspergillosis, zygomycosis can involve the skin alone or may involve other organs, including the gastrointestinal, pulmonary, and central nervous systems. Cutaneous lesions may present as pustules with or without discrete erythematous cellulitis, and they may develop a sharply defined black, necrotic plaque producing a pathognomonic black pus. Vascular invasion can cause ischemia and necrosis. Diagnosis is by tissue biopsy and culture. Treatment includes amphotericin B, but surgical debridement of the lesion is often necessary. The overall mortality of invasive zygomycosis is 64% in neonates.[13]

SYPHILIS

Congenital syphilis, which is caused by *Treponema pallidum*, is divided into early and late disease. Early disease occurs prior to age 3 months. Nearly all infants born to mothers with primary or

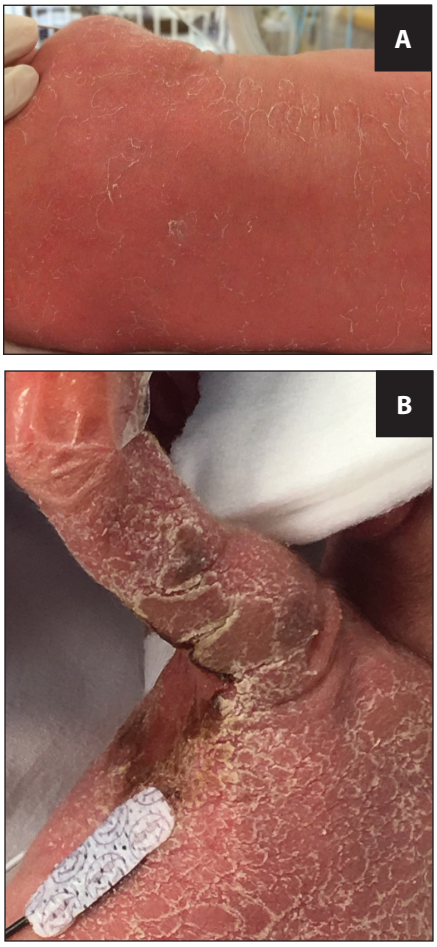

Figure 2. (A) Congenital candidiasis in a full-term infant characterized by erythema with overlying fine collarettes of scale. (B) Invasive fungal dermatitis in a preterm neonate characterized by widespread erythema, thick scale, and erosions in the axilla.

secondary syphilis will acquire the infection and 25% to 40% will die in-utero.[13] About one-half of infected newborns are asymptomatic at birth, with 38% having cutaneous findings.[14] Skin involvement classically involves the perioral, anogenital, and palmoplantar surfaces (**Figure 3**). Although infection rates of congenital syphilis declined from 2008 to 2012, the US Centers for Disease Control (CDC) reported an increase of 28% (to 11.6 per 100,000 live births) in the United States from 2012 to 2014.[14]

The characteristic cutaneous finding is condyloma lata, which appear as flat-topped papules and plaques that occur at the mucocutaneous junctions of the nares, angles of the mouth, and in the anogenital region, and they are highly infectious. Other early skin findings include erythematous papulosquamous plaques, petechiae (from thrombocytopenia), and pemphigus syphiliticus (hemorrhagic vesicles and bullae). Untreated skin lesions typically resolve in 1 to 3 months, often leaving postinflammatory dyspigmentation.

Clear rhinitis (eg, the "syphilitic snuffles") may be the first sign of mucosal involvement and is easily mistaken for a viral upper respiratory infection. Other associated findings include low-birth–weight, hepatomegaly, lymphadenopathy, hydrops fetalis, meningitis, nephrotic syndrome, chorioretinitis, and pseudoparalysis. Radiographic findings are present in up to 95% of symptomatic patients with syphilis and 20% of asymptomatic patients.[15]

T. pallidum cannot be cultured on artificial media, making laboratory diagnosis difficult. Additionally, maternal syphilis IgG is transferred to the fetus, making interpretation of positive tests difficult. Identification relies on four aspects: maternal syphilis identification, maternal treatment, evidence of syphilis in the neonate, and comparison of maternal and neonatal nontreponemal serologic titers.[16] All infants with mothers who have reactive treponemal and nontreponemal tests should have nontreponemal testing (Venereal Disease Research Laboratory test or Rapid Plasma Reagin test). Treponemal tests (*T. pallidum* particle agglutination assay, fluorescent treponemal antibody absorption, and enzyme-linked immunosorbent assay) are difficult to interpret in infants and are not recommended by the CDC.[16]

Cord blood should not be used in tests as it is easily contaminated with maternal blood, which can cause false-positive results. If an infant's nontreponemal test is 4 times greater than the mother's level, then the diagnosis is made and treatment is administered. Clinicians must be aware of the prozone phenomenon in which late maternal acquisition of the disease with resulting high antibody levels interferes with testing and leads to false-negative tests in both the infant and mother. Therefore, when sending samples, the clinician should alert the laboratory to perform prozone testing if the initial result is negative.

Penicillin is the treatment of choice. The most recent treatment guidelines from 2015 can be found on the CDC website.[16]

NEONATAL LUPUS ERYTHEMATOSUS

Neonatal lupus erythematosus (NLE) occurs from the transmission of maternal antibodies through the placenta. The two distinct features of NLE are rash and heart block. Rash occurs in one-half of those affected whereas cardiac involvement affects only about 10%.[17]

The characteristic annular and polycyclic erythematous plaques occur within the first month of life but are not always present. An atrophic appearance, dyspigmentation, scarring, and follicular plugging may be clues to the diagnosis (**Figure 4**). Congenital lesions include ulcerations, bullae, and extensive atrophy. Lesions worsen with ultraviolet light and may present as late as age 6 weeks, but typical skin manifestations can also be found in sun-protected areas, which may confuse and delay diagnosis. Facial lesions are most common around the periorbital ("raccoon eyes") and malar areas as well as the scalp. NLE is often mistaken for eczema, seborrheic dermatitis, or tinea. Topical steroids can hasten resolution and minimize scarring.

Ninety percent of all neonatal heart block is due to NLE.[18] Congenital heart

block is permanent and should be followed closely by a cardiologist. Pacemaker placement in the neonatal period is often required. Other less common systemic associations with NLE include anemia, thrombocytopenia, and cholestatic liver disease.

The initial testing for suspected NLE includes electrocardiogram, complete blood count, and liver function tests in addition to serologic testing in the infant and mother. About 90% of mothers will have positive anti-Ro/SS-A autoantibodies. Anti-La/SS-B and anti-U1RNP autoantibodies are less common. Interestingly, less than 5% of mothers with positive antibodies give birth to affected infants.[17,19] Antibody clearing occurs around age 6 months, although the cutaneous manifestations can persist. Skin biopsy with direct immunofluorescence is usually not necessary but can be used if diagnostic uncertainty exists.

SCLEREMA NEONATORUM

Sclerema neonatorum (SN) affects ill term and premature infants during the first 2 weeks of postnatal life. On occasion, it is seen up to age 4 months in those with severe underlying disease. Thanks to advances in neonatal care, SN has been rarely reported in developed countries over the last decade. In the developing world it continues, likely related to malnutrition, diarrheal disease, low birthweight, and subsequent sepsis.[20]

Cutaneously, there is sudden diffuse hardening of the skin, most commonly around the third day of postnatal life. The skin feels smooth and bound down with immobile joints. This frequently starts in the lower extremities and spreads to the trunk, eventually encompassing most of the body. Notably, SN spares the palms, soles, and genitals. A common characteristic is a "mask-like" appearance of the face.

Infants with SN have an underlying disease and are frequently poorly nourished, dehydrated, hypotensive, hypothermic, and septic.[20] They are at risk for necrotizing enterocolitis, pneumonia, intracranial hemorrhage, and hypoglycemia. The development of this disorder is not well understood but may be a dysfunction causing a depletion of unsaturated fatty acids. Thus, fat solidification occurs more easily and leads to development of the skin findings.

On pathologic examination, the subcutaneous tissue is thick with fibrous bands extending from the fat to the lower dermis. Many laboratory tests are nonspecific for SN, but evaluation of the underlying medical problem should be sought. Those with thrombocytopenia, neutropenia, active bleeding, and worsening acidosis have a worse prognosis. Fatality rates reach as high as 98% if the underlying cause is not treated.[21] By reversing the underlying condition, SN can improve and result in a full recovery without long-term sequelae.

PURPURA FULMINANS

Purpura fulminans is the acute onset of progressive cutaneous hemorrhagic necrosis caused by vascular thrombosis and disseminated intravascular coagulation (DIC). It is secondary to congenital or acquired protein C or S deficiency. Acquired deficiencies occur in neonates that are systemically ill, especially from meningococcal sepsis, varicella, pneumococcal sepsis, and meningitis. Purpura fulminans develops in about 20% of people with meningococcemia.[22]

Initial treatment with a third-generation cephalosporin intravenously should be promptly initiated. Immunocompromised patients also require pseudomonas coverage. If meningococcal disease is the cause, close contacts need appropriate prophylaxis with rifampin or ciprofloxacin. Purpura fulminans can also be caused by numerous other pathogens.

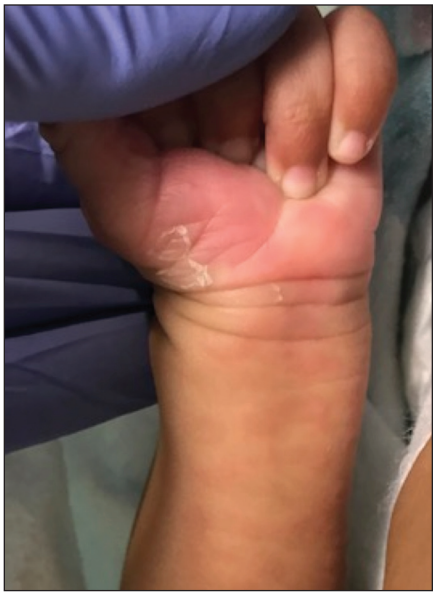

Figure 3. Congenital syphilis in a 2-month-old infant. Note the erythematous papules and plaques on the arm with scaling papules on the palm of the hand.

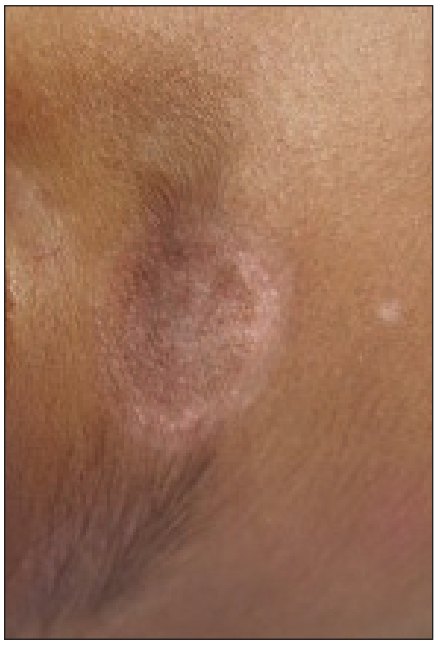

Figure 4. Neonatal lupus erythematosus characterized by dyspigmented plaque with atrophy on the eyebrow of an infant with neonatal lupus.

Purpura fulminans can also be due to a homozygous protein C deficiency or, less commonly, protein S deficiency. Noninfectious causes of purpura in neonates include birth trauma, incompatible blood groups, maternal immune thrombocytopenic purpura, and neonatal isoimmune thrombocytopenia.[23]

Erythema and petechiae initially appear similar to bruising. This rapidly progresses to painful, indurated, well-demarcated, irregularly bordered purpuric papules and plaques surrounded by a thin advancing erythematous border. Late findings include hemorrhagic necrosis. Finally, there is a firm eschar that eventually sloughs. Distal extremities are severely affected and may require surgical intervention.

Shock is characteristically seen, as is systemic consumptive coagulopathy. Elevated partial thromboplastin, partial thromboplastin time, and d-dimers are seen with decreased protein C, S, and antithrombin III. Initial management includes respiratory and hemodynamic support as well as broad-spectrum antibiotics targeting the suspected organisms. Surgical consultation to monitor compartmental pressures is imperative, as is sufficient nutritional support. Those patients with DIC should receive thrombotic support with vitamin K and fresh frozen plasma to correct coagulation factors. Survivors usually have cutaneous and/or skeletal deformities.

BLUEBERRY MUFFIN BABY

"Blueberry muffin baby" is a term used to describe papular or nodular purpura in a neonate. It may be a sign of extramedullary hematopoiesis or direct metastatic infiltration into the skin. Laboratory evaluation and skin biopsy may differentiate the causes of a blueberry muffin rash. The rash was initially described with rubella, although it can be associated with other conditions. **Table 1** outlines the usual causes, including neoplasms as well as extramedullary hematopoiesis.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Staphylococcal scalded skin syndrome (SSSS) is a toxin-mediated disease characterized by cutaneous tenderness and superficial, widespread blistering and/or desquamation. It is a rare cause of erythroderma in the neonate, with most case reports identifying onset within the first week of life.[24] It begins as a generalized macular erythema with accentuation in the flexural and perioral areas (**Figure 5**). The skin acquires a wrinkled appearance leading to desquamation, particularly over a period of 2 to 5 days. In severe cases, this is followed by diffuse, sterile, flaccid blisters and bullous desquamation of large sheets of skin. Denuded areas become apparent where skin has peeled away. This skin is initially moist but as it dries it develops a crusted, flaky appearance. Distinctive radial crusting and fissuring around the eyes, mouth, and nose develop 2 to 5 days after the onset of erythroderma. The significant loss of epidermis makes the patient susceptible to severe secondary infection and fluid loss. Mortality is unusual and is most often due to associated sepsis.

The foci of infection is frequently the nasopharynx or umbilicus. The bacteria produce epidermolytic toxins, which cleave desmoglein I within desmosomes via serine proteases. The disease severity is related to toxin load rather than focal infection; therefore, SSSS is frequently worse in those with reduced renal clearance such as neonates.[25] Isolation of a toxin-producing strain of bacteria with cutaneous findings establishes the diagnosis. Notably, skin bullae are sterile and negative lesional cultures do not rule out SSSS. Nonetheless, cultures should be considered from blood, CSF, urine, nasopharynx, and other suspected sites of infection in attempt to identify the bacteria.

Recovery is usually rapid after systemic antibiotic administration. Treatment with a penicillinase-resistant, antistaphylococcal antibiotic should be initiated, and many favor addition of clindamycin for coverage of methicillin-resistant *Staphylococcus aureus* as well as its ability to inhibit toxin production.[26] A retrospective study suggested that methicillin-susceptible *S. aureus* (MSSA) predominantly cause SSSS, and regional variability of clindamycin-resistant MSSA makes monotherapy problematic.[21] Due to skin fragility, the infant should have minimal handling, and bland emollients to prevent friction and aid in healing should be liberally applied. As the separation is localized to the epidermis, healing occurs without scarring, usually within 14 days.

CONGENITAL VARICELLA

Congenital varicella can be acquired prenatally, perinatally, or postnatally. Lesions from congenital varicella develop in 9 to 15 days after the maternal onset of rash, most commonly maternal primary varicella infections. The most dangerous time for maternal infection is within 2 weeks of delivery. This allows for transfer of the disease placentally without the transfer of maternal antibodies, leaving the infant most susceptible to severe disease. These infants will develop skin lesions 5 to 10 days after delivery. Small pink-to-red macules that rapidly develop a teardrop-shaped vesicle appear. They can also develop into hemorrhagic and/or necrotic vesicles.[27]

Swabs from vesicles, scrapings, biopsy tissue, and CSF for varicella zoster virus can be sent for PCR testing. Once it is known that a pregnant woman has varicella, delaying delivery to allow for transplacental transfer of maternal anti-

TABLE 1.

Causes of "Blueberry Muffin" Rash

Cause	Type	Example
Neoplastic infiltration	Malignant	Leukemia Neuroblastoma
	Nonmalignant	Histiocytosis Transient myeloproliferative disease with or without Down syndrome
Extramedullary hematopoiesis	Anemia	Hereditary spherocytosis Hemolytic disease of the newborn, ABO blood type incompatibility Twin-twin transfusion Bone marrow infiltration/neoplasm
	Infection	Rubella Toxoplasmosis Cytomegalovirus Parvovirus

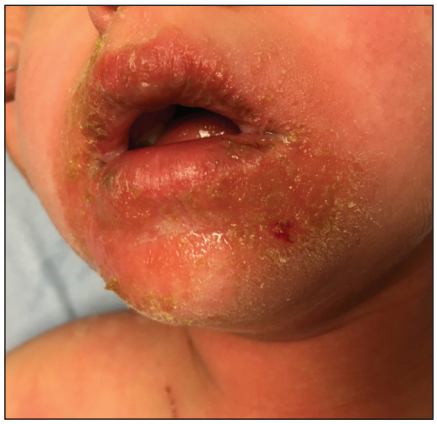

Figure 5. Infant with staphylococcal scalded skin syndrome. There is radial crusting and fissuring periorally with background erythema.

bodies is ideal. Prior to the use of acyclovir, mortality was as high as 30% due to severe pneumonitis and respiratory distress.[28] Neonates should receive varicella zoster immune globulin immediately after birth. Infants can breast-feed if they can avoid contact with maternal lesions. Symptomatic neonates should receive intravenous acyclovir for 10 days. Therapy for up to 21 days may be required for CSF dissemination. The use of prophylactic acyclovir is currently being debated.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV), a viral infection that occurs in up to 2% of all births,[29] is acquired congenitally, perinatally, or postnatally. CMV antibodies increase with age.[30] Women in many developing countries have near 100% seroconversion by childbearing age;[31] but in the United States only about 60% of women have anti-CMV antibodies by their teenage years.[31] Most infections are clinically silent. A primary infection acquired in-utero poses a much higher risk than one occurring later in childhood or adulthood. The severity of the infection and symptoms vary with trimester, with earlier gestational infections being worse. Skin lesions seen with CMV are extramedullary hematopoiesis (blueberry muffin rash) and petechiae similar to congenital rubella findings. These resolve in the first few weeks of life. Other findings can include intrauterine growth retardation, hepatosplenomegaly, jaundice, thrombocytopenia, microcephaly, cerebral atrophy, chorioretinitis, hearing loss, and periventricular intracerebral calcifications.

When evaluating for CMV, samples may be collected from the urine, pharynx, saliva, blood, and other tissues and sent for culture or PCR testing. A congenital infection will have positive results in the first 2 weeks of life. Of note, perinatal CMV has a uniformly good outcome whereas congenital CMV has a poor prognosis.[32]

Additional serologic studies can be used to differentiate perinatal and congenital CMV. CMV-IgM in cord blood verifies congenital infection, although this has low sensitivity. PCR testing for CMV-DNA in the neonate is highly sensitive. Treatment is recommended for those with significant symptoms to prevent progression to hearing loss and involves ganciclovir for 6 weeks or valganciclovir for many months.

CONCLUSION

Dermatologic emergencies in newborns require rapid diagnosis and treatment. The conditions reviewed here are often initially managed by ambulatory pediatricians or emergency department physicians prior to the input of a dermatologist. The knowledge and swift action of the pediatrician in the conditions discussed significantly affects the outcome, including morbidity and mortality.

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